UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,345	06/19/2003	Andreas Gerardus Uitterlinden	ERUR121089	5017

26389 7590 01/22/2007

CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC
1420 FIFTH AVENUE
SUITE 2800
SEATTLE, WA 98101-2347

EXAMINER	
SALMON, KATHERINE D	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,345	UITTERLINDEN ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8-12,21,24,29,30 and 34-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6, 8-12, 21, 24, 29, 30, 34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 12/22/2006. Currently, Claims 6, 8-12, 21, 24, 29-30, and 34-36 are pending.

2. The finality of the previous office action mailed 9/26/2006 has been withdrawn based on arguments that the previous office action incorporated new art not necessitated by amendment.

3. The following rejections are applied as necessitated by amendment or are reiterated. Response to arguments follows.

4. This action is FINAL.

Withdrawn Rejections

5. The rejection of Claims 6, 8-11, 21, 24, 29-31, and 33 under 35 USC 112/2nd paragraph made at section 8 of the previous office action, is moot in view of the amendments to the claims.

6. The rejection of Claims 12 and 32 under 35 USC 102(b) made at section 10 of the previous office action, is moot in view of the amendments to the claims.

7. The rejection of Claim 6, 9-11, and 29-31 under 35 USC 103(a) made at section 12 of the previous office action is moot in view of the arguments made in the reply. Specifically, the specification combination of the haplotype of px and the homozygous haplotype baT is not obvious over the teaching in the art, which independently assesses the alleles.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 6, 8-11, 21, 24, 29-31, and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining susceptibility to vertebral BMD independent fracture in a Caucasian female subject said method comprising analyzing nucleic acid molecules obtained from the human subject to determine which of the P, p, X, and x alleles of the estrogen receptor gene are present, and further comprising determining the copy number of a member of the group consisting of the P, p, X, and x alleles of the estrogen receptor gene and the B, b, A, a, T, and t alleles of the vitamin D receptor gene, and determining that the subject has an increase susceptibility to vertebral BMD if the subject has a haplotype comprising a px haplotype and a homozygous baT haplotype does not reasonably provide enablement for determining the susceptibility of ANY BMD independent fracture nor a method of

treating or recommending a treatment regimen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claim 6 is drawn to a method of determining susceptibility to bone mineral density (BMD) independent fracture compromising determining the presence of px and a homozygous haplotype baT and the copy number. Claims 8-9 are drawn to a method performed in vitro and on a blood or tissue sample. Claim 10 is drawn to a subject suffering from low bone mineral density. Claim 11 is drawn to a mammalian subject, which has a normal level of bone mineral density. Claim 21 is drawn to a method of formulating a treatment regimen to decrease the risk of bone fracture in a mammalian subject comprising determining if the px and homozygous baT haplotype is present. Claim 24 is drawn to administering a treatment effective to decrease the risk of BMD independent fracture. Claims 29 and 30 are drawn to a method to determine

susceptibility of a bone fracture wherein the presences of the haplotype is determined by amplification of a portion of the first intron of the estrogen receptor alpha gene and amplification of the portion of the vitamin D receptor gene between exon 7 and 3' untranslated region. Claim 31 and 33 define the baT allele as homozygous. Claims 34-36 define the BMD-independent fracture as a vertebral fracture.

The claims are drawn to methods of determining ANY BMD-independent fracture with haplotypes of px and the homozygous haplotype of baT. The claims are drawn to a method of formulating ANY treatment regime.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts unexpected associations between specific Estrogen Receptor alpha gene (ERα) and vitamin D receptor (VDR) genotypes and the vertebral fracture (p. 3 lines 9-11). The specification does not teach an association of the ERα and VDR genotypes with ANY BMD independent fracture. BMD independent fractures include any type of fracture of any of the bones. It would be unpredictable that every bone fracture would have the same association with the two genotypes.

The specification asserts that risk of susceptibility to bone damage is independent of bone mineral density (p. 9 lines 28-30). The specification asserts that there is a correlation between individuals with the p and x alleles and susceptibility to

bone fractures (p. 11 lines 8-11). The specification asserts a subject having the px haplotype in ERα and a haplotype of BAt or baT for the VDR polymorphisms is susceptible to bone fractures (p. 11 lines 13-14). Bat and baT haplotypes do not appear to distinguish susceptibility.

The specification teaches the preferred method of treatment is prescribing or administering an agent that reduces the susceptibility of a subject to bone fracture (p. 15 lines 15-16). The specification lists examples such as administering sodium alendronate, parathryoid hormone, anabolic steroids, or vitamin D preparations (p. 15 lines 18-20). The specification teaches a method of treating a population, but does not teach a method of recommending a treatment regimen to decrease the risk of bone fracture. It is unclear if ANY treatment regimen decreases the risk of bone fracture. Further, the steps to recommend a treatment regimen are not provided by the specification. It is unpredictable that ANY formulated treatment regimen would decrease the risk of bone fracture. It is unclear which treatment regimens are effective to decrease the risk of BMD independent fractures in a population with a specific allelic type.

It is unpredictable to recommend ANY treatment regiment by analyzing the genotype. The skilled artisan would have to perform undue experimentation in order to provide the necessary steps to recommend a treatment regimen from a genotypic analysis.

Working Examples

The specification provides an example that asserts the polymorphisms in the ERα gene and the VDR gene are positively correlated with increased susceptibility to bone fracture in human beings (p. 23 lines 1-4).

The specification asserts women are grouped according to carrier status for the ER alpha and VDR haplotypes as homozygous carriers (genotype 11) and heterozygous carriers (genotypes 12 and 13) in table 3 (p. 27 lines 12-16). Table 3 lists the p values for lumbar spine BMD and femoral neck BMD (p. 28). The only significant p values are observed in data of the lumbar spine BMD with HOMOZYGOUS VDR haplotype (p value <0.001) and the combination of HOMOZYGOUSE VDR and HOMOZYGOUS ER alpha haplotypes (p value 0.05) (p. 28 Part A of Table 3).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there are a significant number of parameters, which would have to be studied. The skilled artisan would have to determine the relationship of the ER alpha (px) and the VDR (baT) haplotype for any type of BMD independent bone fracture. Further the specification only teaches a statistically significant association between the homozygous baT allele and the combination of the homozygous baT and homozygous px alleles in lumbar spine breaks, the specification does not teach this association with any other BMD independent bone fracture. The skilled artisan would need to determine if an association could be made in ANY BMD independent bone fracture breaks. The skilled artisan would need to determine the steps involved with making a treatment regimen

based on the genetic testing of baT and px. The skilled artisan would have to determine the effect of the allelic association with treatment plan.

This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where There are many genetic factors influencing BMD independent fractures which may be different dependent on fracture location. Given there is no support in the specification for the formulation of the steps of Any treatment regimen. Given the broad claims in an art whose nature is identified as unpredictable, and the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been amended such that the claims now encompass formulating treatment regimen based on a genotypic analysis and risk factor (p. 8 last paragraph). The response asserts that the specification provides support for vertebral fractures wherein women are heterozygous or homozygous for px and homozygous for baT (p. 9 1st paragraph). The response asserts the claims are not determining "any bond fracture" but only BMD-independent fracture.

Though there is an association between px and the homozygous baT in Caucasian women for vertebral fractures, there is no correlative evidence that the same association may be made with any BMD independent fractures.

There is no clear association of any treatment regime with the genotypic analysis. It is unclear how to recommend a treatment regime based on genotypic analysis. It is unclear if treatment regime is affected by the results of genotypic analysis and how the skilled artisan would in fact factor the genotypic results in to a treatment regime recommendation.

Conclusion

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Katherine Salmon
Examiner
Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER